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Review Article

Refractory Migraine – A Review

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Refractory migraine has long been a challenge to all headache specialists. This subgroup of migraine patients experience disability and impaired quality of life, despite optimal treatment. This article reviews the proposed definitions and epidemiology of refractory migraine, as well as the pathophysiology that may contribute to the genesis of this disorder. Aspects of treatment, including pharmacological, complementary/adjunct, and invasive approaches, are reviewed. Comorbid factors, medication overuse, potential pitfalls to treatment, and areas for future investigation are highlighted.

Key words: refractory, migraine, definition, abuse, placebo, headache

Abbreviations: AHS American Headache Society, BTA onabotulinumtoxinA, CBT cognitive–behavioral therapy, CM chronic migraine, DHE dihydroergotamine, EM episodic migraine, HCP health care providers, MIDAS Migraine Disability Assessment, MOH medication overuse headaches, ONS occipital nerve stimulation, OSA obstructive sleep apnea, OTC over-the-counter, QoL quality of fife, R-CM refractory chronic migraine, RH refractory headache, RHSIS Refractory Headache Special Interest Section, RM refractory migraine, SE side effects, TTH tension-type headache

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INTRODUCTION

The refractory migraine (RM) patient has long been a challenge to all headache specialists. While chronic migraine (CM) substantially impairs quality of life (QoL),[1] the RM patient may experience greater disability. This article will discuss the proposed definitions, epidemiology, as well as postulated mechanisms that may contribute to the genesis of RM. Lacking evidence-based interventions, empiric treatment approaches are discussed, including specific pharmacological, complementary/adjunct, and psychological approaches, as well as interventional procedures. Combining the various modalities, where possible, will improve the likelihood of successful treatment.

All comorbid factors should be addressed, especially sleep and mood disorders. Avoiding medication overuse and emphasizing patient "wellness" are essential. A trusting physician–patient relationship is the key and will enhance compliance and foster communication. In those RM patients with multiple comorbidities, a multidisciplinary team should optimize management. A special section is devoted to treatment suggestions and avoiding pitfalls that are common in RM. Future areas of focus include the need for a consensus-based definition. Only with a standardized definition will evidence-based treatments be identified, and the epidemiology be characterized. Areas which are promising for future

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research include the effect of placebo and expectation, whether childhood abuse contributes to refractoriness, disease modification, the role of mood and cervical dysfunction, and further investigation of the pathophysiology using newer imaging tools.

DEFINITION OF RM

Headache specialists have recognized this subgroup of patients who remain refractory to treatment, despite optimal abortive and preventive treatment. Some health care providers (HCP) intuitively define patients as "refractory" by looking at a long list of failed abortive and preventive medications. The Refractory Headache Special Interest Section (RHSIS) was formed in 2000. Although various definitions were considered by the section, no consensus was reached (L. Robbins, personal communication).

Few formal definitions for RM or intractable migraine have been proposed (Table 1). Crafting an operational definition for RM is challenging. Issues include the degree of intractability, level of disability, number of failed medications required to be considered refractory, and the subsequent appropriate intervention after being labeled refractory. If the threshold for failure is high, the patient may be a candidate for a more aggressive level of care, such as inpatient treatment utilizing a multidisciplinary team approach. If the threshold for failure is lower, they may qualify for a less ambitious approach.

Schulman and Traumata proposed a definition for refractory headache (RH).[2] It included the following: (1) headaches occurring at least 15 days per month; (2) lack of responsiveness to multiple preventive medications, given in appropriate doses over a sufficiently reasonable period of time; (3) no analgesic rebound. This early definition (proposed in 1993) ignored disability, what constituted failure, and does not suggest optimizing mood and lifestyle.

A more comprehensive definition for intractable headache addressed both migraine and cluster types.[3] Criteria include failing an adequate trial of regulatory approved and conventional treatments, according to local and national guidelines. To be considered intractable, one would need to fail 4 different cluster or migraine preventive agents. Failure would allow patients to be considered for more invasive treatment

Table 1.—Criteria for Definitions of Refractory Headaches

Authors	Prophylactic medications	Acute medications	Adequate dose of medication	Adequate length of time of medication	Frequency/ length of headache	Disability	Analgesic overuse	Comorbid disorders addressed	Level of refractiveness	Addressed migraine only	Stratified patients for clinical practice ± trials
Goadsby et al[3]	■	—	■	■	—	—	■	—	—	—	—
Schulman and Traumuta[2]	■	—	■	■	■	—	■	—	—	—	—
Schulman et al[6]	■	■	■	■	—	■	■	■	—	■	—
Silberstein et al[5]	■	■	■	■	—	■	■	—	■	—	■
Robbins†[7]	■	■	■	■	—	■	■	■	■	■	—

†Used RHSIS criteria.
Black squares signify criteria addressed in proposed definition.

such as occipital nerve stimulation (ONS) for migraine and deep brain stimulation or ONS for cluster headache.

The definition proposed by RHSIS includes optimizing comorbid conditions, addressing triggers and lifestyle factors, and failing an adequate trial of both preventive and abortive medications. Modifiers included the presence or absence of medication overuse and degree of disability[4] (Table 2). The authors of this definition focused on episodic migraine (EM) and CM because of their high prevalence. Addressing additional primary headache disorders would add complexity.

Table 2.—Proposed Criteria for Definition of Refractory Migraine and Refractory Chronic Migraine

Criteria	Definition
Primary diagnosis	A. ICHD-II migraine or chronic migraine
Refractory	B. Headaches cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy 1. Failed adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes: a. β-blockers b. Anticonvulsants c. Tricyclics d. Calcium channel blockers 2. Failed adequate trials of abortive medicines from the following classes, unless contraindicated: a. *Both* a triptan *and* DHE intranasal or injectable formulation b. *Either* nonsteroidal anti-inflammatory drugs *or* combination analgesics
Adequate trial	Period of time during which an appropriate dose of medicine is administered, typically at least 2 months at optimal or maximum-tolerated dose, unless terminated early due to adverse effects
Modifiers	With or without medication overuse, as defined by ICHD-II With significant disability, as defined by MIDAS $\geq$ 11

DHE = dihydroergotamine; ICHD = International Classification of Headache Disorders; MIDAS = Migraine Disability Assessment.

More recently, a definition was proposed that stratified refractory patients into levels of intervention. Levels of severity were based on the failure of both acute and preventive agents and degree of disability.[5] A commentary from RHSIS addressed the proposal.[6]

Robbins raised the challenges in defining RM and suggested a rating scale for degree of refractoriness.[7] RM patients were followed over a 10-year period and those having the most severe RM remained more disabled and experienced more pain than those in those with milder RM.[8]

A survey of the members of the American Headache Society (AHS) agreed that a definition for RM is needed (91%), and that it should be added to the International Classification of Headache Disorders (87%).[9] Currently, there is no worldwide consensus on any one definition.

EPIDEMIOLOGY

Twelve percent of the US population experiences EM[10] with the US prevalence of CM approximately 1%.[11] Headaches in 370 consecutive patients attending a headache clinic in a tertiary centers were classified using the criteria proposed by the RHSIS.[12] Nineteen (5.1%) of the patients evaluated had RM, with a mean age of 43. Of the RM group, 58% were female. In the remainder of patients seen, 46.4% had migraine and 20.8% had tension-type headache (TTH). The rest had other primary or secondary headaches. Seventy-nine percent of the refractory group had refractory chronic migraine (R-CM), and 21% had RM. Thirty-six percent of the refractory patients had medication overuse headaches (MOH). R-CM patients had more disability than RM, with R-CM with MOH having significantly higher Migraine Disability Assessment (MIDAS) (mean 131.6) than R-CM without MOH (mean 95).

PATHOPHYSIOLOGY

Migraine is a complex disorder that involves multiple pathways and numerous neuropeptides. Mechanistic considerations may hold some answers as to why RM develops. At present, the exact pathophysiology of RM is unknown. Brain systems and functions that may yield insight into the etiology of

RM include impaired modulation and cortical hyperexcitability, structural changes, genetic heterogeneity, or differences in receptor binding.[13]

Evidence suggests that there is a deficiency of inhibition or increased facilitation of migraine pain.[14] RM may be perceived as a disorder of the failure of the mechanisms that terminate migraine attacks. The successful identification of mechanisms responsible for the cessation of migraine attacks may allow for a better understanding of the pathophysiology of migraine and lead to novel mechanisms to enhance headache termination.[15]

Cortical excitability may be raised in CM. Atypical pain perception and processing may explain why migraine attacks are often triggered by lights, visual patterns, noise, and odors. There is also a positive correlation between intensity of headache pain and intensity of photophobia, phonophobia, and osmophobia. This increased susceptibility to migraine triggers results in increased frequency of attacks.[16] Cutaneous allodynia, a marker of central sensitization, is more frequent in patients who have a long history of CM. Allodynia is also correlated with the frequency of migraine attacks.[17-19] Whether hyperexcitability contributes to RM, is unknown.

There is now good evidence that childhood maltreatment is a risk factor for migraine and headache chronification. Abuse is an area which often impacts RM patients.[20-22] Considerable preclinical and clinical evidence demonstrates that early life stress results in long-term changes in the sympathetic nervous system and hypothalamo-pituitary-adrenocortical axis, the principal pathways that respond to stress, and are also important in migraine.[23-25]

A postulated explanation why 30% of migraineurs are triptan nonresponsive is genetic heterogeneity of the 5HT-1D/1B receptors.[26] These differences may influence the resulting pathways that are activated in the blood vessel and neurons that are activated in response to triptan binding, and lead to failure of abortive medication.

WHEN TREATING RM, ALWAYS BEGIN WITH THE BASICS

Risk factors have been identified associated with the causation of CM.[27] Although these may not be operational in causing RM, it is reasonable to address them in patients who have RM. They include:

Mood Disorders.—*Ask Specifically About Anxiety, Worrying, Panic Disorder, Depression, or Bipolar Disease.*—Asking the patient's companion, spouse, or other family member about the patient's mood is helpful. Always create an opportunity where you can question the patient about their mood when they are alone. This is particularly important in adolescents.

Unless trained in the area of psychiatry, it can be challenging to appropriately identify mood disorders. Some migraineurs report "stress," but this may be an indicator of anxiety, a panic disorder, or depression. All patients should be required to complete an inventory that can assist in identifying "masked" depression, such as the Beck Depression Test or Zung Self-Rating Anxiety Scale. Although clinical depression may be evident, the degree of depression may be underestimated.

The most common trigger for migraine is emotional stress.[28] The anxiety associated with frequent migraine and its disability may act as a trigger, and this bidirectional influence can lead to increased impairment in RM.

Mood disorders can contribute to headache progression. There is ample evidence that psychiatric comorbidity is a factor that contributes to the progression from EM to both CM and RM.[29] Anxiety and depression contribute to poor compliance, and when the treatment is not optimally effective, the anxious tend to overuse medications.[30] Impaired mood may also induce or amplify pain.[31] Mood disorders may also render RM patients more refractory to preventive therapy as a result of epigenetic changes in pain transmission circuits.

MOH.—RM patients may often present with MOH because of self-treatment with near daily use of over-the-counter (OTC) analgesics. Oftentimes, RM patients develop MOH, particularly when they are prescribed multiple abortive medications (first line, second line, and rescue medications) and ignore the frequency guidelines for abortive usage. Most practitioners feel detoxification is of crucial importance in those with medication overuse.[32] Others feel it should be encouraged, but is not mandatory.[33] Regardless, educating the patient about medication overuse is paramount.

Most agree that opioids should be prescribed only for rescue and in limited quantities. Some, however, use methadone for patients with CM who have failed to respond to more conventional treatment.[34] Besides the issue of safety, chronic opioid use may result in more frequent and more intense headache.[35-37] Opioids cause a paradoxical increase in pain sensitivity,[38] and individuals with EM who use opiates are at increased risk of progression to CM.[39] Further, chronic opioid therapy provides meaningful relief in only 10-15% of patients who receive it.[40] Even after opioid withdrawal, the MOH is less likely to remit, is more likely to relapse, and is less responsive to preventive agents.[36,41] Continuous opioid therapy should be used in rare circumstances for CM[42] or RM.

Sleep Disorders.—Sleep and headache are intimately related. Over- or under sleeping may cause headache, and yet, sleep may relieve headache. Common sleep disorders associated with headache include obstructive sleep apnea (OSA), periodic leg movement disorder, insomnia, hypersomnia, and circadian rhythm disorders. Headache upon awakening is common with OSA.[43-47] Insomnia, the most common sleep disorder associated with headache, may reflect anxiety. In patients with chronic RH who also had OSA, continuous positive airflow pressure treatment alone does not seem to improve headache, but further study was suggested.[48] Screen for sleep disorders and if indicated, evaluate with a polysomnogram.

PHARMACOLOGICAL TREATMENT

The choice of abortive and preventive agents should be based on evidence-based guidelines. Begin with those that have shown established or probable efficacy in EM.[49] The proposed RHSIS definition[4] can serve as a paradigm for HCP treating headache patients which have been labeled as refractory. This definition includes required treatment thresholds that can be applied in clinical practice. Be sure the patient has had an adequate trial of the drug before excluding it. It is important to determine if the drug was ineffective, or side effects (SE) were excessive. Sometimes patients discontinue medications because of the fear of a potential SE. In some cases, a medication may be retried, but at low doses and with close physician monitoring.

Only rarely do medications become ineffective because of the development of tolerance. Pharmacodynamic tolerance is characterized by decreased effectiveness of the drug unrelated to its concentration. Tachyphylaxis, the rapid development of complete tolerance to the medication, is based on receptor desensitization. Cross-tolerance occurs when one drug becomes ineffective, and a second drug with a similar mechanism of action, although unique from the first, also exhibits tolerance.[50] Migraine preventives also become ineffective as a result of additional mechanisms, including placebo effect, variability in disease expression or progression, inaccurate recall, or drug delivery problems.[51]

When headaches become more frequent, be certain that the patient is compliant. Sometimes RM patients discontinue their preventives because their headaches became less frequent, believed they were "cured," or are simply tired of taking daily medication. Re-educating the patient about the role of the preventive is often necessary.

When there is uncertainty why relapse has occurred, one option is a short drug holiday or to rotate drugs. When a patient develops tolerance to a series of drugs after several months of effective treatment, consider initiating another drug prior to developing tolerance to the first. Drugs may overlap as the second drug is titrated up to a therapeutic level, followed by a slow taper of the first. Combination therapy, another option, should utilize drugs with different mechanisms of action that may also be effective in treating comorbid issues.

An early treatment approach utilized in patients who have less than an optimal response to abortive agents is polytherapy.[52,53] The combination of intravenous (IV) prochlorperazine and dihydroergotamine (DHE) is highly effective when used as a rescue treatment in the emergency room.[54] Peroutka discussed "rational polytheraputic approaches to migraine" by utilizing several agents in combination, each targeting a distinct pathway of migraine.[55] These systems included dopaminergic hypersensitivity, inflammation, and "low" 5-hydroxytryptamine. "Triple

therapy" employed a dopamine agonist, an anti-inflammatory agent, and a triptan.[56] Clinical trials demonstrated that the combination of sumatriptan 85 mg and naproxen 500 mg were synergistic and more effective than 100 mg of sumatriptan alone.[55] Combining sumatriptan with metoclopramide provided relief in some migraineurs who failed to achieve adequate relief with a triptan alone.[57] Saadah[58] compared DHE and prochlorperazine, in varying doses, to DHE 1 mg alone. DHE 1 mg and prochlorperazine 10 mg were superior to DHE 1 mg alone. Variability in the study design and lack of head-to-head studies make it difficult to compare one combination therapy against another.[59]

Several reviews have advocated the use of combination therapy in migraine prevention.[56] Some have suggested using polypharmacy to manage migraine and comorbid disorders.[60,61] Combination therapy has also been shown to be more effective in migraine prevention than one drug alone (Table 3). All the agents that were used in combination treatment have shown established or probable efficacy, with the exception of flunarizine. The 3 studies which reported positive results[62-64] used "failure of monotherapy with multiple agents"[63] or "failure when both agents were used separately"[62,64] as the definition of refractory. However, 2 of the 3 positive trials were open label. Notably, the 2 negative trials used CM as the inclusion criteria.[65,66] Will R-CM migraine patients experience poorer outcomes with combination therapy than RM? Is failing monotherapy a predictor of a positive result when agents are used in combination? There are also important questions, and rigorous trials are necessary.

Several unique agents have shown efficacy in migraine. Only those recently cited in the literature are included. These include ketamine,[67] memantine,[68] propofol,[69] quetiapine,[70] and clonazepam.[71] IV lidocaine, long used to treat headache, has also shown some promising results.[72] All these reports are open label, and most had a small sample size.

Table 3.—Combination Therapy Treatments for Headache Prevention

Authors	Agents used	Inclusion criteria	Study design	Results
Pascual et al 2003[63]	β-blockers and valproate	Failed monotherapy with multiple agents	Open label	56% had >50% reduction in migraine headache days
Pascual et al 2007[64]	β-blocker and topiramate	Failed both agents when used separately	Open label	60% had >50% reduction in headache frequency
Krymchantowski et al 2011[62]	Nortriptyline and topiramate	Failed both agents when used separately	Randomized placebo-controlled trial	Significant decrease in number of headache days compared with baseline while on 2 drugs
Silberstein et al 2012[66]	Propranolol and topiramate	CM at least 10 days/month	Randomized placebo-controlled trial	No significant change in multiple endpoints
Luo et al 2012[65]	Flunarizine and topiramate vs each drug individually	CM	Open label	No significant change in mean monthly migraine frequency

CM = chronic migraine.

INTERVENTIONAL PROCEDURES

Local procedures, with the exception of botulinum toxin, have not been subject to blinded placebo-controlled trials. Study outcomes are vulnerable to

expectations, conditioning, and the natural history of this waxing and waning disorder.

Peripheral Nerve Blocks.—Peripheral nerve blocks should be considered in the RM patient, especially those with a poor response to medication.[73] Temporary relief with local analgesics may engage secondary mechanisms and achieve long-term benefit.[74] Common blocks include those of the greater and lesser occipital, auriculotemporal, supraorbital, and supratrochlear nerves. Peripheral nerve blocks may be administered either for acute treatment or at regular intervals.

Botulinum Toxin Injections.—Botulinum toxin type A is a protein that inhibits the release of acetylcholine from presynaptic nerve endings and inhibits the release of calcitonin gene-related peptide and substance P. OnabotulinumtoxinA (BTA) is the only agent approved for CM. Two phase 3 clinical trials support the efficacy of BTA for CM, including those overusing acute headache medications.[75,76] BTA was compared with topiramate,[77,78] and improvement was similar in the 2 groups. In an open trial on R-CM patients, BTA reduced the frequency of disabling attacks and the consumption of triptans.[79]

Nerve Stimulation.—ONS is utilized for various chronic refractory primary headache disorders.[80,81] Published trials suggest a possible benefit in those with chronic daily headache and CM. Studies are ongoing in an attempt to further define the benefit. As with all interventions, lack of proper blinding impairs assessment of true efficacy. A combination of ONS and supraorbital neurostimulation was used to treat CM and R-CM. In the small group treated, results were positive and better than ONS alone.[82] Vagus nerve stimulation was utilized in 4 female patients who had "drug refractory" CM and depression. Preliminary results support a beneficial effect for both CM and depression.[83] An R-CM patient treated with an implanted auriculotemporal nerve stimulator experienced decreased pain intensity and had improved function at 16 months.[84] Transcranial magnetic stimulation is effective and well tolerated in migraine with and without aura.[85,86] Repeated use in RM patients not studied.

Migraine Surgery.—"Migraine surgery" has been performed by some plastic surgeons. One randomized, placebo-controlled trial that involved "surgical deactivation" of frontal, temporal, and occipital trigger sites showed 84% improvement at 12 months vs 58% in the sham group.[87] The migraine patients in the study were not classified as refractory or intractable. In an earlier study,[88] patients received Botox injections in the supercilii muscle. Patients who experienced complete elimination of migraine had these muscles surgically resected. In the surgical group, 95% observed postoperative improvement. Of the patients who improved, 45.5% reported complete elimination of headache. One reviewer suggested blinding Botox injection and including sham surgery as a control before this surgery is recommended.[89]

Sinus Surgery.—During migraine attacks, nasal mucosa may become swollen in a subset of patients. The resulting edema can increase the pressure between opposing nasal surfaces and results in pain. Patients should be carefully evaluated prior to any surgical separation.[90]

ADJUNCT TREATMENTS

Patient "wellness" should be emphasized. Good sleep hygiene includes maintaining regular hours and not oversleeping on weekends. Avoid skipping meals and eat in a healthy manner. Exercising, while not shown to be effective, can serve to relieve stress and provides important "me" time.[91]

The use of nonpharmacological treatments, unaccompanied by other first line agents, are rarely effective in the treatment of RM. Recent migraine guidelines report good scientific evidence for petasites and fair scientific evidence for riboflavin, magnesium, and feverfew,[92] but none have been evaluated in RM.

Address Obesity.—Obesity is associated with EM and CM.[93] Studies suggest that weight loss is associated with a decline in migraine frequency.[94] Avoid, if possible, preventive medications that predispose to weight gain.

Caffeine Excess.—Patients with CM tended to use more caffeine than those with EM.[95] Caffeine is present in many OTC and prescription combination analgesics. It is also present in coffee, teas, soft drinks, chocolate, and energy drinks. The caffeine content in coffee can vary from 107 mg (home brewed) to 330 mg

(Starbucks Grande). As little as one caffeinated beverage per day may precipitate headache upon withdrawal.[96] The role of caffeine in RM is unknown.

Behavioral Treatment.—Relaxation biofeedback and cognitive–behavioral therapy (CBT) are reasonable treatment options for migraine prevention. CBT, when combined with a taper of the medication responsible for rebound and the addition of preventive drug therapy, adds additional benefit. CBT is effective for anxiety and obsessive–compulsive disorder, commonly comorbid with migraine. Psychotherapy can assist in reducing some of the sequelae of abuse. Biofeedback, in conjunction with a reduction of the overused medication and the initiation of preventive therapy, can reduce the relapse rates of MOH.[97,98] Behavioral treatment may serve to reduce stressors and improve mood.

"PEARLS" OF RM TREATMENT

"Don't rest until you test."[99] The diagnosis of RM is based on ruling out the presence of pathology which can account for the headache.

Keeping a headache calendar is in essential for optimal management. Pay particular attention to headache triggers, patterns, and whether there is medication overuse.

Discuss reasonable goals and expectations. A realistic goal is to decrease disability and improve QoL. Emphasize that improvement will be slow, and sometimes there will be "speed bumps" in the recovery process.

Patient education is essential. Patients who were supplied with education materials reported improvement in their headache frequency, as well as the cognitive and emotional aspects of headache management.[100] Those who participated in an intensive migraine education program exhibited a significant reduction in their MIDAS scores compared with those treated with medical management alone.[101]

Recognize the problem patient early.[99] Patients with personality disorders are particularly challenging. The angry or overly solicitous patient, or those whose level of pain is incongruous with their appearance or social functioning, are potential warning signs.

Be a cheerleader and always have another plan. If you give up, so will your patient. However, if the patient is becoming discouraged, the HCP may encourage a second opinion from a trusted headache expert. This gives them implicit "permission" to leave or seek a new assessment. Sometimes a fresh perspective can provide diagnostic possibilities that previously not considered.

Identify medication misuse and the problems that underlie it.[99] Some RM patients overuse medications because they are unable to control pain. Others utilize medications to treat anxiety, because of their fear of headaches, or as a result of a true addictive behavior. Identifying why patients overuse medication and addressing the cause are essential.

Set strict limits. Compliance is imperative. Patients must take responsibility for their disorder. Insist that only one physician make changes in medications or treatment modalities. When a multidisciplinary team is utilized, decisions should be made in a collaborative fashion.

GOING FORWARD

Future areas of focus include the need for a consensus-based definition. Additionally, research of promising concepts may assist in achieving optimal treatment of RM (Table 4).

A consensus-based definition.—Our treatment and understanding of RM will be enhanced by a consensus-based definition which has worldwide acceptance. It will allow us to:

- Assist RM patients in obtaining the appropriate level of care. Meeting the criteria of the definition may expedite referral to a headache specialist,

Table 4.—Our Treatment and Understanding of RM Will Be Enhanced By

A consensus-based definition which has worldwide acceptance
Optimally addressing mood
Routinely screening for abuse and maltreatment
Emphasizing the effect of placebo and expectation in doctor–patient interactions
Clarifying the pathophysiology using newer imaging modalities
Further evaluation of disease modification
Clarifying the role cervical dysfunction

RM = refractory migraine.

enlisting a multidisciplinary approach, or inpatient treatment.
- Better characterize the disorder, including its epidemiology and identifying unmet medical needs.
- Identify the "Best Practices" treatment.
- Serve as the criteria for inclusion in studies utilizing novel pharmacological approaches. Using the definition as inclusion criteria for invasive treatment trials, with a higher threshold for failure than for pharmacological trials, is a reasonable option.

Optimally Addressing Mood.—Anxiety and depression are more common in patients with CM compared with those EM.[1] Migraine in association with various mental health disorders results in poorer health-related outcomes compared with migraine or a psychiatric condition alone.[102]

In a survey of AHS members by the RHSIS, respondents included "addressing extraordinary stress" and "recognizing and managing comorbid disorders such as depression" as suggested "Best Practices" for RM patients. Suggest a psychiatric or psychological referral when patients are suicidal or severely depressed. A willing and skilled psychiatrist or psychologist can aid in clarifying the psychiatric diagnosis and serve as a valuable collaborator. Biofeedback and CBT can be helpful in managing stress.[103]

Routinely Screening for Abuse and Maltreatment.—There is now good evidence that childhood maltreatment is a risk factor for EM and headache chronification.[20,104,105] Prior or ongoing abuse is also associated with comorbid mood disorders. Adverse childhood experiences result in long-term changes in the principal pathways involved in both stress and migraine.[23-25] These changes may predispose to progression to RM. Improved understanding of the role of abuse and its relationship to painful states is an area which deserves further research.

All patients should be routinely screened for past or ongoing abuse.[106] Identifying abuse may influence the assessment and treatment of headache. Consequences can be treatment failures. All abused patients should receive appropriate resources and referrals.

Emphasizing the Effect of Placebo and Expectation in Doctor–Patient Interactions.—Placebos are prescribed by about half of US internists and rheumatologists.[107] When using a placebo to treat migraine patients abortively, a positive headache response was present in 7% to 50% of patients, with an average placebo response rate of 30%.[108] Although the responder rate is lower for migraine preventives than in acute treatment for migraine, a meta-analysis of 32 studies found that the pooled placebo response rate for migraine preventives was 21%.[109]

Table 5.—Qualities Which Enhance the Placebo Response[126]

The physician
• Shows empathy
• Shows compassion
The patient
• Seeks relief from a symptom
• Admires the physician for their skills and virtues
• Is hopeful
• Trusts the physician
• Interprets nonverbal communication of the physician (gestures, posture, and facial expressions) as positive

Psychological or neurobiological mechanisms underlie the placebo response. Psychological aspects include expectancy and conditioning, with some postulating their coexistence. Neurobiological mechanisms are mediated both by opioid and nonopioid systems.[110] Imaging has demonstrated changes in the pain matrix following placebo administration.[111]

The placebo response is highly influenced by the expectations of the clinician and the patient as well as the patient–clinician interaction itself (Table 5). Context has an important influence on the outcome of treatment and may affect the course of painful conditions. There is an improved response when the practitioner is positive about the prospects of treatment.[112]

> "A lot of this [the placebo effect] is about what people used to call the art of being a physician. Our system is geared to undermine this. Doctors are not paid for their time; they're paid for what they do. We probably could achieve the same effects (as placebo) simply by having doctors talk to their patients more," Jonathan Moreno, PhD[113]

Patient expectations also affect their perception of pain.[114] Opioid receptors modulate neurons in a circuit that selectively controls nociceptive transmis-

sion. This circuit can operate in both pain-inhibiting and pain-facilitating states. There is growing evidence that the state of the circuit is determined by aversive and appetitive motivational states. With strong emotion (fear, anger, elation) major injuries may be painless. When pain is anticipated, pain may occur or worsen even in the absence of noxious stimulation. How the clinician's actions, words, gestures, and the patient's expectations influence the illness in RM is an area suitable for further evaluation.

Clarifying the Pathophysiology Using Newer Imaging Modalities.—Further elucidation of the pathophysiology can be accomplished using sophisticated imaging such as functional magnetic resonance imaging (MRI), positron emission tomography, or voxel-based morphometry MRI studies. Research using these techniques have focused on CM or medication overuse. They have shown change in the "pain matrix" in CM compared with EM (A. Charles, personal communication). Some speculate that the genesis of RM is related to these structural and functional changes in the pain matrix that occur over time. Investigating the differences in hypersensitivity symptoms and multisensory processing in both EM and RM may provide further insights into the pathophysiology of RM.

Further Evaluation of Disease Modification.—For some patients, migraine is a chronic progressive disease.[115] Repeated episodes of migraine are associated with permanent changes in central nervous system structure, including iron accumulation in the periaqueductal gray matter[116] and changes to the visual cortex.[117] Patients with migraine had a higher incidence of cerebellar infarction, with rates being higher in those with aura compared with those in migraine without aura.[118] Some have postulated that the MRI abnormalities reflect cumulative brain insults because of repeated attacks.[115] Yet some RM patients spontaneously remit.[119]

There is an increased risk for progression in those who experience 3 or more headaches per month. Early use of preventive treatment may prevent transformation from migraine to CM.[120] More than 40% of migraineurs may benefit from prevention yet only 13% of migraine sufferers receive it.[121] For others, preventive treatments may be effective, even after discontinuation.

The "Biomarker Project" project initiated by the AHS may assist in predicting the course of migraine and gauging the patient's risk for developing RM. Disease modification for those at high risk of progression is a promising option.

Does early abortive treatment, using novel combinations of preventive therapy, avoiding risk factors or infrequent use of opioids modify the course of migraine? These are all important questions for further research.

Clarifying the Role of Cervical Dysfunction.—Neck symptoms often accompany migraine and TTH.[122,123] Referral of head pain from upper cervical structures is a result of the convergence of C1, C2, C3, and trigeminal nociceptive afferent information to the trigeminocervical nucleus. When sustained pressure was applied to the lateral posterior arch of C1 and the articular pillar of C2, head pain referral was reported by 100% of TTH participants (n = 14), and 19 of 20 (95%) migraineurs and 8 of 14 (57%) control participants.[124] Ten participants of the control group experienced infrequent non-migrainous headache. Head pain was produced in 8 of the 10 when cervical pressure was applied. The mechanism of cervical afferents affecting neurons in the trigeminal nuclei might contribute to migraine, TTH, and those with infrequent headache.[96]

The role of noxious cervical afferents may well be significantly underestimated. Saper and Lake report "that the C_2-C_3 zone is a 'therapeutic window' and that a 'block' may induce a pain modulatory stimulus rather than a blockade."[125] Study of this mechanism may contribute to the understanding of the pathophysiology of RM and generate novel treatment options.

CONCLUSIONS

RM patients pose a challenge for all practitioners. These patients experience both disability and impaired QoL. Yet the recent attention this group has received has stimulated interest in the field and has resulted in additional proposed RM definitions and both pharmacological and invasive trials that address RM. Successfully treating RM patients requires

enlisting all of the modalities and refining them. Identification of "Best Practices" and further defining the pathophysiology will benefit all headache patients.

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REFERENCES

1. Buse D, Manack A, Serrano D, et al. Headache impact of chronic and episodic migraine: Results from the American Migraine Prevalence and Prevention Study. *Headache*. 2012;52:3-17.
2. Schulman EA, Traumuta G. Refractory headache [abstract]. *Headache*. 1993;33:273-286.
3. Goadsby P, Schoenen J, Ferrari M, Silberstein S, Dodick D. Towards a definition of intractable headache for use in clinical practice and trials. *Cephalalgia*. 2006;26:1168-1170.
4. Schulman EA, Lake AE III, Goadsby PJ, et al. Defining refractory migraine and refractory chronic migraine: Proposed criteria from the Refractory Headache Special Interest Section of the American Headache Society. *Headache*. 2008; 48:778-782.
5. Silberstein SD, Dodick DW, Pearlman S. Defining the pharmacologically intractable headache for clinical trials and clinical practice. *Headache*. 2010;50:1499-1506.
6. Schulman EA, Lipton R, Peterlin BL, Levin M, Grosberg BM. Commentary from the refractory headache special interest section on defining the pharmacologically intractable headache for clinical trials and clinical practice. *Headache*. 2010;50:1637-1639.
7. Robbins L. Refractory headache definition. *Headache*. 2011;51:310-311.
8. Robbins L. Refractory chronic migraine: Long-term follow-up using a refractory rating scale. *Headache*. 2012;13:225-229.
9. Schulman EA, Peterlin BL, Lake AE 3rd, et al. Defining refractory migraine: Results of the RHSIS Survey of American Headache Society members. *Headache*. 2009;49:509-518.
10. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349.
11. Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: Results from the American Migraine Prevalence and Prevention study. *Headache*. 2012;52:1456-1470.
12. Irimia P, Palma JA, Fernandez-Torron R, Martinez-Vila E. Refractory migraine in a headache clinic population. *BMC Neurol*. 2011;11:94.
13. Goadsby PJ, Hargreaves R. Medically refractory primary headache: Some mechanistic considerations. In: Schulman EA, ed. *Refractory Migraine*. New York: Oxford University Press; 2010:46-57.
14. Vanegas H, Schaible HG. Descending control of persistent pain: Inhibitory or facilitatory? *Brain Res Brain Res Rev*. 2004;46:295-309.
15. Shapiro RE. How do migraine attacks stop? *Headache*. 2012;52:191-192.
16. Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A. Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and positron emission tomography studies*. *Headache*. 2007;47: 996-1003.
17. Ashkenazi A, Sholtzow M, Shaw J, Burstein R, Young WB. Identifying cutaneous allodynia in chronic migraine using a practical clinical method. *Cephalalgia*. 2007;27:111-117.
18. Mathew NT, Kailasam J, Seifert T. Clinical recognition of allodynia in migraine. *Neurology*. 2004; 63:848-852.
19. Schoenen J, De Klippel N, Giurgea S, et al. Almotriptan and its combination with aceclofenac for migraine attacks: A study of efficacy and the influence of auto-evaluated brush allodynia. *Cephalalgia*. 2008;28:1095-1105.
20. Tietjen GE, Brandes JL, Peterlin BL, et al. Childhood maltreatment and migraine (part I). Prevalence and adult revictimization: A multicenter headache clinic survey. *Headache*. 2009;50:20-31.
21. Monahan K, O'Leary K. Head injury and battered women: An initial inquiry. *Health Soc Work*. 1999; 24:269-278.
22. Felitti VJ, Anda RF. A program of health presentations. Available at: http://www.ACEStudy.org (accessed November 19, 2012).
23. Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: Role of childhood trauma. *Biol Psychiatry*. 2008; 63:398-405.
24. Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of

child abuse and neglect. *Dev Psychobiol*. 2010;52: 671-690.
25. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. *Neurosci Biobehav Rev*. 2003;27:33-44.
26. Pauwels PJ. Diverse signaling by 5-hyroxytryptamine (5-HT) receptors. *Biochem Pharmacol*. 2000;60:1743-1750.
27. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression. *Headache*. 2006;46:1334-1343.
28. Andress-Rothrock D, King W, Rothrock J. An analysis of migraine triggers in a clinic-based population. *Headache*. 2010;50:1366-1370.
29. Baskin SM, Lipchik GL, Smitherman TA. Mood and anxiety disorders in chronic headache. *Headache*. 2006;46:S76-S87.
30. Mitsikostas D, Thomas A. Comorbidity of headache and depressive disorders. *Cephalalgia*. 2002; 19:211-217.
31. Dodick DW. Reflections and speculations on refractory migraine: Why do some patients fail to improve with currently available therapies? *Headache*. 2008;48:828-837.
32. Olesen J. Detoxification for medication overuse headache is the primary task. *Cephalalgia*. 2012;32: 420-422.
33. Diener HC. Detoxification for medication overuse headache is not necessary. *Cephalalgia*. 2011;32: 423-427.
34. Rothrock JF. Treatment-refractory migraine: The case for opioid therapy. *Headache*. 2008;48: 850-854.
35. Angst MS, Clark JD. Opioid-induced hyperalgesia: A qualitative systematic review. *Anesthesiology*. 2006;104:570-587.
36. Mao J. Opioid-induced abnormal pain sensitivity. *Curr Pain Headache Rep*. 2006;10:67-70.
37. Ossipov MH. Opioids in the treatment of headache: Perspective from the bench. *Headache Currents*. 2006;3:53-62.
38. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: Molecular mechanisms and clinical considerations. *Clin J Pain*. 2008;24: 479-496.
39. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: A longitudinal population-based study. *Headache*. 2008;48:1157-1168.
40. Saper JR, Lake AE 3rd, Hamel RL, et al. Daily scheduled opioids for intractable head pain: Long-term observations of a treatment program. *Neurology*. 2004;62:1687-1694.
41. Zeeberg P, Olesen J, Jensen R. Probable medication-oversue headache: The effect of a 2-month drug-free period. *Neurology*. 2006;66: 1894-1898.
42. Saper JR, Lake AE III. Continuous opioid therapy (COT) is rarely advisable for refractory chronic daily headache: Limited efficacy, risks, and proposed guidelines. *Headache*. 2008;48:838-849.
43. Dodick DW, Eross EJ, Parish JM, Silber M. Clinical, anatomical, and physiologic relationship between sleep and headache. *Headache*. 2003;43: 282-292.
44. Rains JC. Chronic headache and potentially modifiable risk factors: Screening and behavioral management of sleep disorders. *Headache*. 2008;48:32-39.
45. Rains JC, Poceta JS. Headache and sleep disorders: Review and clinical implications for headache management. *Headache*. 2006;46:1344-1363.
46. Rains JC, Poceta JS. Sleep and headache. *Curr Treat Options Neurol*. 2010;12:1-15.
47. Sancisi E, Cevoli S, Vignatelli L, et al. Increased prevalence of sleep disorders in chronic headache: A case-control study. *Headache*. 2010;50:1464-1472.
48. Mitsikostas D, Vikelis M, Viskos A. Refractory chronic headache associated with obstructive sleep apnoea syndrome. *Cephalalgia*. 2008;28:139-143.
49. Silberstein S, Holland S, Freitag F, Dodick D, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345.
50. Rizzoli P, Loder EW. Tolerance to the beneficial effects of prophylactic migraine drugs: A systematic review of causes and mechanisms. *Headache*. 2011;51:1323-1335.
51. Loder EW, Rizzoli P. Tolerance and loss of beneficial effect during migraine prophylaxis: Clinical considerations. *Headache*. 2011;51:1336-1345.
52. Lance JW. Headache. *Ann Neurol*. 1981;10:1-10.

53. Wilkinson M. Treatment of the acute migraine attack – current status. *Cephalalgia*. 1983;3:61-67.
54. Callaham M, Raskin N. A controlled study of dihydroergotamine in the treatment of acute migraine headache. *Headache*. 1986;26:168-171.
55. Peroutka SJ. Beyond monotherapy: Rational polytherapy in migraine. *Headache*. 1998;38:18-22.
56. Krymchantowski AV, Bigal ME. Polytherapy in the preventive and acute treatment of migraine: Fundamentals for changing the approach. *Expert Rev Neurother*. 2006;6:283-289.
57. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache*. 2003;43:729-733.
58. Saadah HA. Abortive headache therapy in the office with intravenous dihydroergotamine plus prochlorperazine. *Headache*. 1992;32:143-146.
59. Kelley NE, Tepper DE. Rescue therapy for acute migraine, part 2: Neuroleptics, antihistamines, and others. *Headache*. 2012;52:292-306.
60. Silberstein SD, Dodick D, Freitag F, et al. Pharmacological approaches to managing migraine and associated comorbidities – clinical considerations for monotherapy versus polytherapy. *Headache*. 2007;47:585-599.
61. Peterlin BL, Calhoun AH, Siegel S, Mathew NT. Rational combination therapy in refractory migraine. *Headache*. 2008;48:805-819.
62. Krymchantowski AV, da Cunha Jevoux C, Bigal ME. Topiramate plus nortriptyline in the preventive treatment of migraine: A controlled study for nonresponders. *J Headache Pain*. 2012;13:53-59.
63. Pascual J, Leira R, Láinez J. Combined therapy for migraine prevention? Clinical experience with a beta-blocker plus sodium valproate in 52 resistant migraine patients. *Cephalalgia*. 2003;23:961-962.
64. Pascual J, Rivas M, Leira R. Testing the combination beta-blocker plus topiramate in refractory migraine. *Acta Neurol Scand*. 2007;115:81-83.
65. Luo N, Di W, Zhang A, et al. A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. *Pain Med*. 2012;13:80-86.
66. Silberstein SD, Dodick DW, Lindblad AS, et al. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. *Neurology*. 2012;78:976-984.
67. Krusz JC, Cagle J, Scott-Krusz VB. Ketamine for treating multiple types of headaches. *Cephalalgia*. 2009;29(Suppl. 1):151-152.
68. Bigal M, Rapoport A, Sheftell F, Tepper D, Tepper S. Memantine in the preventive treatment of refractory migraine. *Headache*. 2008;48:1337-1342.
69. Soleimanpour H, Taheraghdam A, Rajaei Ghafouri R, Taghizadieh A, Marjany K, Soleimanpour M. Improvement of refractory migraine headache by propofol: Case series. *Int J Emerg Med*. 2012;5:19.
70. Krymchantowski AV, Jevoux C. Quetiapine for the prevention of migraine refractory to the combination of atenolol + nortriptyline + flunarizine: An open pilot study. *Arq Neuropsiquiatr*. 2008;66:615-618.
71. Maizels M. Clonazepam for refractory headache: Three cases illustrative of benefit and risk. *Headache*. 2010;50:650-656.
72. Rosen N, Marmura M, Abbas M, Silberstein S. Intravenous lidocaine in the treatment of refractory headache: A retrospective case series. *Headache*. 2009;49:286-291.
73. Ashkenazi A, Levin M. Nerve blocks, neurostimulation, and botulinum toxin injection treatment for refractory migraine. In: Schulman EA, Levin M, Lake AE III, Loder E, eds. *Refractory Migraine Mechanisms and Management*. New York: Oxford University Press; 2010:266-292.
74. Afridi S, Shields K, Bhola R, Goadsby P. Greater occipital nerve injection in primary headache syndromes – prolonged effects from a single injection. *Pain*. 2006;122:126-129.
75. Aurora S, Dodick D, Turkel C, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*. 2010;30:793-803.
76. Diener H, Dodick D, Aurora S, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010;30:804-814.
77. Cady RK, Schreiber CP, Porter JAH, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. *Headache*. 2010;51:21-32.
78. Mathew NT, Jaffri SFA. A double-blind comparison of onabotulinumtoxinA (BOTOXA®) and

topiramate (TOPAMAXA®) for the prophylactic treatment of chronic migraine: A pilot study. *Headache*. 2009;49:1466-1478.
79. Oterino A, Ramon C, Pascual J. Experience with onabotulinumtoxinA (BOTOX) in chronic refractory migraine: Focus on severe attacks. *Headache*. 2011;12:235-238.
80. Lambru G, Matharu MS. Occipital nerve stimulation in primary headache syndromes. *Ther Adv Neurol Disord*. 2012;5:57-67.
81. Saper JR, Dodick DW, Silberstein SD, et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia*. 2011;31:271-285.
82. Reed K, Black S, Banta C, Will K. Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: Initial experience. *Cephalalgia*. 2010;30:260-271.
83. Proietti Cecchini A, Mea E, Tullo V, et al. Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: Preliminary data. *Neurol Sci*. 2009;30:101-104.
84. Simopoulos T, Bajwa Z, Lantz G, Lee S, Burstein R. Implanted auriculotemporal nerve stimulator for the treatment of refractory chronic migraine. *Headache*. 2010;50:1064-1069.
85. Clarke BM, Upton AR, Kamath MV, Al-Harbi T, Castellanos CM. Transcranial magnetic stimulation for migraine: Clinical effects. *J Headache Pain*. 2006;7:341-346.
86. Lipton RB, Dodick DW, Silberstein SD, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: A randomised, double-blind, parallel-group, sham-controlled trial. *Lancet Neurol*. 2010;9:373-380.
87. Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S. A placebo-controlled surgical trial of the treatment of migraine headaches. *Plast Reconstr Surg*. 2009;124:461-468.
88. Guyuron B, Tucker T, Davis J. Surgical treatment of migraine headache. *Plast Reconstr Surg*. 2002; 109:2183-2189.
89. Guyuron B, Tucker T, David J. Surgical treatment of migraine headaches. *Headache*. 2003;43: 302-303.
90. Behin F, Lipton RB, Bigal M. Contact points and migraine headaches. In: Clarke LB, ed. *Migraine Disorders Research Trends*. New York: Hauppauge Nova Science Publishers, Inc.; 2007:1-15.
91. Busch V, Gaul C. Exercise in migraine therapy – is there any evidence for efficacy? A critical review. *Headache*. 2008;48:890-899.
92. Holland S, Silberstein S, Freitag F, Dodick D, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78: 1346-1353.
93. Evans RW, Williams MA, Rapoport AM, Peterlin BL. The association of obesity with episodic and chronic migraine. *Headache*. 2012;52:663-671.
94. Peterlin BL. Bariatric surgery in obese migraineurs: Mounting evidence but important questions remain. *Cephalalgia*. 2011;31:1333-1335.
95. Scher AI, Stewart WF, Lipton RB. Caffeine as a risk factor for chronic daily headache: A population-based study. *Neurology*. 2004;63:2022-2027.
96. Griffiths R, Evans S, Heishman S, et al. Low-dose caffeine physical dependence in humans. *J Pharmacol Exp Ther*. 1990;255:1123-1132.
97. Grazzi L, Andrasik F, D'Amico D, et al. Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse: Outcome at 3 years. *Headache*. 2002;42:483-490.
98. Grazzi L, Andrasik F, Usai S, Bussone G. Headache with medication overuse: Treatment strategies and proposals of relapse prevention. *Neurol Sci*. 2008;29:93-98.
99. Saper JR. Pearls from an inpatient headache unit. *Headache*. 2008;48:820-827.
100. Smith TR, Nicholson RA, Banks JW. Migraine education improves quality of life in a primary care setting. *Headache*. 2010;50:600-612.
101. Rothrock JF, Parada VA, Sims C, Key K, Walters NS, Zweifler RM. The impact of intensive patient education on clinical outcome in a clinic-based migraine population. *Headache*. 2006;46: 726-731.
102. Jette N, Patten S, Williams J, Becker W, Wiebe S. Comorbidity of migraine and psychiatric disorders – a national population-based study. *Headache*. 2008;48:501-516.
103. Sauro KM, Becker WJ. The stress and migraine interaction. *Headache*. 2009;49:1378-1386.
104. Tietjen GE, Brandes JL, Peterlin BL, et al. Childhood maltreatment and migraine (part II). Emo-

tional abuse as a risk factor for headache chronification. *Headache*. 2009;50:32-41.
105. Tietjen GE, Brandes JL, Peterlin BL, et al. Childhood maltreatment and migraine (part III). Association with comorbid pain conditions. *Headache*. 2009;50:42-51.
106. Schulman EA, Hohler AD. The American Academy of Neurology position statement on abuse and violence. *Neurology*. 2012;78:433-435.
107. Tilburt JC, Emanuel EJ, Kaptchuk TJ, Curlin FA, Miller FG. Prescribing "placebo treatments": Results of national survey of US internists and rheumatologists. *BMJ*. 2008;337:a1938.
108. Bendtsen L, Mattsson P, Zwart JA, Lipton RB. Placebo response in clinical randomized trials of analgesics in migraine. *Cephalalgia*. 2003;23:487-490.
109. Macedo A, Banos JE, Farre M. Placebo response in the prophylaxis of migraine: A meta-analysis. *Eur J Pain*. 2008;12:68-75.
110. Finniss DG, Benedetti F. The neural matrix of pain processing and placebo analgesia: Implications for clinical practice. *Headache Curr*. 2005;2:132-138.
111. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia-imaging a shared neuronal network. *Science*. 2002;295:1737-1740.
112. Benedetti F. How the doctor's words affect the patient's brain. *Eval Health Prof*. 2002;25:369-386.
113. Valeo T. Why neurologists prescribe placebos. *Neurology Today*. 2008;8:13-14.
114. Fields H. State-dependent opioid control of pain. *Nat Rev Neurosci*. 2004;5:565-575.
115. Lipton RB, Pan J. Is migraine a progressive brain disease? *JAMA*. 2004;291:493-494.
116. Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: Cause or the burden of illness? *Headache*. 2001;41:629-637.
117. Chronicle E, Mulleners W. Might migraine damage the brain? *Cephalalgia*. 1994;14:415-418.
118. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. *JAMA*. 2004;291:427-434.
119. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain*. 2003;106:81-89.
120. Loder E, Biondi D. General principles of migraine management: The changing role of prevention. *Headache*. 2005;45:S33-S47.
121. Lipton RB, Diamond M, Freitag FG, Bigal ME, Stewart WF, Reed ML. Migraine Prevention Patterns in a Community Sample: Results from the American Migraine Prevalence and Prevention (AMPP) Study. Headache 45:792, 2005. Presented at the 47th Annual Scientific Meeting of the American Headache Society, Philadelphia, PA, June 23-25, 2005.
122. Blau JN, MacGregor EA. Migraine and the neck. *Headache*. 1994;34:88-90.
123. Silberstein SD. Tension-type headaches. *Headache*. 1994;34:S2-S7.
124. Watson DH, Drummond PD. Head pain referral during examination of the neck in migraine and tension-type headache. *Headache*. 2012;52:1226-1235.
125. Saper JR, Lake AE III. Inpatient strategies for refractory migraine. In: Shulman EA, Levin M, Lake AE III, Loder E, eds. *Refractory Migraine: Mechanisms and Management*. New York: Oxford University Press; 2010:314-340.
126. Benedetti F. *The Patient's Brain: The Neuroscience Behind the Doctor-Patient Relationship*. New York: Oxford Universtiy Press; 2011.